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Ten false beliefs about cortisol in critically ill patients

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Activation of the hypothalamo–pituitary–adrenal (HPA) axis, an integral component of the stress response, results in an increase in plasma cortisol concentrations. In critical illness, a syndrome of relative adrenal insufficiency (RAI) has been proposed, which is thought to be associated with a worse outcome [1]. Measurements of plasma cortisol and the response to cosyntropin are used to assess adrenocortical function in critical illness. It is important that clinicians are aware of the fallacies associated with this approach in determining adrenocortical function in critical illness [2].

A lower plasma total cortisol value is associated with a worse outcome

The premise of RAI is that an increase in plasma cortisol in response to a critical illness may not be of sufficient magnitude for the severity of the stimulus that engendered it. This suggests that random cortisol estimations in septic shock should be over a minimum threshold value to ensure the response is adequate. What constitutes an appropriate baseline cortisol in the critically ill patient is unclear. Studies have demonstrated a wide range of elevated total plasma cortisols in stressed ICU patients. If the premise of RAI is accurate, then this should translate to an increase in observable mortality associated with plasma cortisol values at the lower end of the range seen in critical illness. However, multiple studies have demonstrated that the reverse is true: higher random cortisol values are associated with a greater mortality in septic shock [2].

A single measurement of plasma cortisol gives a valid estimation of the 24 h average cortisol level

Examination of spontaneous fluctuations of total plasma cortisol in critically ill patients shows substantial hour-to-hour variation; this may be greater than that seen with cosyntropin stimulation [3]. This may result from erratic release of pituitary ACTH. This level of variability means that interpretation of a single random total cortisol measurement is problematic.

Total cortisol assays are interchangeable

Total plasma cortisol is commonly measured by immunoassays. These exhibit differing degrees of cross-reactivity to steroids other than cortisol. In stressed patients, there is a generalized increase in steroid secretion and the effects of cross-reactivity are exaggerated. The same sample when analyzed by different assays can

return substantially different results, often leading to inconsistencies in the classification of adrenal insufficiency [4].

The incremental response of total plasma cortisol to cosyntropin stimulation is a reliable indicator of adrenal function and a predictor of outcome

A reduced increment of plasma cortisol of <250 nmol/L following cosyntropin is commonly described as being diagnostic of RAI and predictive of outcome. Although the test may be indicative of adrenal function in certain circumstances, controversy exists with respect to the optimal dose of cosyntropin, end points for assessment: total or free cortisol, the effect of plasma cortisol variability, basal cortisol and adrenal blood flow on the cortisol response, and finally its equivalence with other tests of adrenocortical function [5]. There is no consistent relationship between cortisol response and illness severity in critical illness. Importantly, subgroup analysis of randomised controlled trials of steroids in septic shock do not consistently report a benefit of steroids even in the group purported to have RAI [6, 7].

A high increment on the cosyntropin test rules out adrenal insufficiency

A substantial increment on the cosyntropin test has commonly been suggested as a marker of an appropriately functioning HPA axis. However, there are clear situations where a high increment occurs in the presence of clinically significant adrenal insufficiency. An example would be recent damage to the hypothalamus or pituitary following traumatic brain injury or intracerebral hemorrhage. Some of these patients may be left ACTH-deficient and thus hypoadrenal but the adrenal gland retains responsiveness to exogenous ACTH for up to 3 weeks [8]. Similar hypotheses have been put forward in patients with sepsis, although precise data on incidence of this phenomena in this condition are not available [9].

Total plasma cortisol concentrations accurately reflect the bioavailable fraction—plasma free cortisol (PFC)

In health, 95 % of circulating cortisol is protein bound, primarily to corticosteroid binding globulin (CBG) and 5 % is free (the bioactive fraction), but this may be a more valid measure of adrenal function. In critical illness, there is a decline in CBG concentrations and affinity leading to a relative increase in PFC, which is not reflected in the total concentration. Discordance between total and PFC estimations is evidenced by the relatively greater increase in PFC in patients with septic shock compared to controls, and in the far greater relative increment of PFC to cosyntropin stimulation [10].

Calculation of PFC concentrations is an acceptable alternative to direct measurement

Direct measurement of free cortisol is complex, time consuming and not widely available. Calculation of PFC concentrations using the Coolen's equation is unreliable in critical illness. This method assumes a constant binding affinity of CBG to cortisol, and does not account for albumin binding, nor for the competing effect of other steroid molecules. Comparisons of direct measurement with calculated PFC in critically ill patients have demonstrated significant errors of bias and imprecision between the two methods [11].

Plasma cortisol concentrations accurately reflect intracellular concentrations

Glucocorticoids exert their biological effects by passing through the cell membranes and binding to intracellular receptors. Intracellular cortisol concentrations are modulated by several enzymes involved in glucocorticoid metabolism such as the 11β hydroxysteroid dehydrogenases (11β-HSD), type 1 and type 2 and the A-ring reductases [12]. The former enzymes are responsible for the interconversion of active cortisol and inactive cortisone, whilst the latter are involved in cortisol clearance. In critical illness, there is evidence of altered 11β-HSD and suppressed A-ring reductase activity [13]. These in turn could impact on intracellular concentrations, thus making it difficult to assess the tissue adrenal response based on a plasma cortisol.

Elevated cortisol concentrations are primarily due to increased glucocorticoid production

The increase in plasma cortisol concentrations have been traditionally attributed entirely to increased production. Recent studies, however, have suggested that a reduction in cortisol clearance may also be an important contributor. Decreased clearance may occur by downregulation of

cortisol metabolizing enzymes in the liver and adipose tissue caused by elevated bile acid levels [13, 14].

Treatment with 'stress doses' of hydrocortisone in critically ill patients with suspected hypoadrenalism results in physiological cortisol levels

The typical 'replacement' dose of hydrocortisone in severely ill patients is 50–100 mg every 8 h. This may lead to grossly supraphysiological levels of cortisol [15], and is in part due to the reduced cortisol clearance seen in many critically ill patients [14]. Whether lower doses of glucocorticoids should be administered in this situation has not been adequately explored in clinical trials.

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. Annane D, Sebille V, Troche G et al (2000) A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. JAMA 283:1038–1045
2. Cohen J, Venkatesh B (2010) Relative adrenal insufficiency in the intensive care population; background and critical appraisal of the evidence. Anaesth Intensive Care 38(3):425–436
3. Venkatesh B, Mortimer RH, Couchman B et al (2005) Evaluation of random plasma cortisol and the low dose corticotropin test as indicators of adrenal secretory capacity in critically ill patients: a prospective study. Anaesth Intensive Care 33(2):201–209
4. Cohen J, Ward G, Prins J et al (2006) Variability of cortisol assays can confound the diagnosis of adrenal insufficiency in the critically ill population. Intensive Care Med 32:1901–1905
5. Venkatesh B, Cohen J (2014) The utility of the corticotropin test to diagnose adrenal insufficiency in critical illness: an update. Clin Endocrinol (Oxf) (in press)
6. Annane D, Sebille V, Charpentier C et al (2002) Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 288:862–871
7. Sprung CL, Annane D, Keh D et al (2008) Hydrocortisone therapy for patients with septic shock. N Engl J Med 358:111–124
8. Hjortrup A, Kehlet H, Lindholm J, Stentoft P (1983) Value of the 30-minute adrenocorticotropin (ACTH) test in demonstrating hypothalamic–pituitary–adrenocortical insufficiency after acute ACTH deprivation. J Clin Endocrinol Metab 57:668–670
9. Marik PE, Zaloga GP (2002) The central nervous system hypothalamic–pituitary–adrenal axis in sepsis. Crit Care Med 30:490–491
10. Hamrahian AH, Oseni TS, Arafah BM (2004) Measurements of serum free cortisol in critically ill patients. N Engl J Med 350:1629–1638
11. Cohen J, Venkatesh B, Tan T (2013) Comparison of the diagnostic accuracy of measured and calculated free cortisol in acutely ill patients using the Coolens equation. Crit Care Resusc 15:39–41
12. Rabbitt EH, Lavery GG, Walker EA, Cooper MS, Stewart PM, Hewison M (2002) Prereceptor regulation of glucocorticoid action by 11beta-hydroxysteroid dehydrogenase: a novel determinant of cell proliferation. FASEB J 16:36–44
13. Boonen E, Vervenne H, Meersseman P et al (2013) Reduced cortisol metabolism during critical illness. N Engl J Med 368:1477–1488
14. Boonen E, Van den Berghe G (2014) Cortisol metabolism in critical illness: implications for clinical care. Curr Opin Endocrinol Diabetes Obes 21:185–192
15. Keh D, Boehnke T, Weber-Carstens S, Schulz C, Ahlers O, Bercker S, Volk HD, Doecke WD, Falke KJ, Gerlach H (2003) Immunologic and hemodynamic effects of 'low-dose' hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study. Am J Respir Crit Care Med 167:512–520